Acute Blood Pressure Reduction in Patients With Intracerebral Hemorrhage Does Not Result in Borderzone Region Hypoperfusion

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on behalf of the ICH ADAPT Investigators

Background and Purpose—The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT) demonstrated blood pressure (BP) reduction does not affect mean perihematoma or hemispheric cerebral blood flow. Nonetheless, portions of the perihematoma and borderzones may reach ischemic thresholds after BP reduction. We tested the hypothesis that BP reduction after intracerebral hemorrhage results in increased critically hypoperfused tissue volumes.

Methods—Patients with Intracerebral hemorrhage were randomized to a target systolic BP (SBP) of <150 or <180 mm Hg and imaged with computed tomographic perfusion 2 hours later. The volumes of tissue below cerebral blood flow thresholds for ischemia (<18 mL/100 g/min) and infarction (<12 mL/100 g/min) were calculated as a percentage of the total volume within the internal and external borderzones and the perihematoma region.

Results—Seventy-five patients with intracerebral hemorrhage were randomized a median (interquartile range) of 7.8 (13.3) hours from onset. Acute hematoma volume was 17.8 (27.1) mL and mean SBP was 183±22 mm Hg. At the time of computed tomographic perfusion (2.3 [1.0] hours after randomization), SBP was lower in the <150 mm Hg (n=37; 140±18 mm Hg) than in the <180 mm Hg group (n=36; 162±12 mm Hg; P<0.001). BP treatment did not affect the percentage of total borderzone tissue with cerebral blood flow <18 (14.7±13.6 versus 15.6±13.7%; P=0.78) or <12 mL/100 g/min (5.1±5.1 versus 5.8±6.8%; P=0.62). Similar results were found in the perihematoma region. Low SBP load (fraction of time with SBP<150 mmHg) did not predict borderzone tissue volume with cerebral blood flow <18 mL/100 g/min (β=0.023 [-0.073, 0.119]).

Conclusions—BP reduction does not increase the volume of critically hypoperfused borderzone or perihematoma tissue. These data support the safety of early BP reduction in intracerebral hemorrhage.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00963976. (Stroke. 2014;45:2894-2899.)

Key Words: cerebral hemorrhage ▼ hypertension ▼ perfusion imaging

Intracerebral hemorrhage (ICH) is associated with acute hypertension and the management of blood pressure (BP) in the early phase of ICH is controversial.1 Although it is hypothesized that aggressive acute BP reduction may reduce hematoma expansion, concern remains that this may exacerbate cerebral ischemia and infarction, particularly in vulnerable tissues, such as the perihematoma region and watershed territories.2

In the recently completed ICH Acutely Decreasing Arterial Pressure Trial (ICH ADAPT),3 we demonstrated that BP reduction does not affect mean perihematoma or hemispheric cerebral blood flow (CBF). Recent MRI study results suggest the possibility of ischemia within borderzone (watershed) territories after ICH.4–10 It is unknown whether CBF within the borderzone regions reaches ischemic thresholds. In this secondary, post hoc analysis of ICH ADAPT data, we tested the hypothesis that BP reduction was associated with an increased volume of critically hypoperfused tissue, within the borderzone regions, using computed tomographic perfusion (CTP) thresholds for CBF, cerebral blood volume (CBV), and mean

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transit time. We also assessed the effect of low BP load on borderzone perfusion.

**Methods**

**Patients**

The ICH ADAPT protocol (clinicaltrials.gov NCT00963976) has been published previously.21 Briefly, patients aged ≥18 years presenting with acute primary ICH diagnosed on noncontrast CT (NCCT) scan within 24 hours of symptom onset were prospectively enrolled. Exclusion criteria included evidence of secondary ICH, planned surgical resection, contraindications to BP reduction or indication for urgent reduction, or inability to undergo CTP imaging. Informed consent was obtained from each patient or an authorized representative, and human ethics committees at each site approved the study protocol.

**BP Management and Analysis**

Intravenous antihypertensive agents (labetalol/hydralazine/enalapril) were used to achieve target systolic BP (SBPs) within 1 hour of randomization. BP and heart rate were measured noninvasively every 15 minutes during active BP treatment and every 30 minutes thereafter until the time of the CTP. National Institutes of Health Stroke Scale scores were recorded at baseline, 2 hours, 24 hours, and at 90 days. Weighted average BPs were calculated as the area under the curve describing pressures >24 hours, as previously described.21 Low SBP load (fraction of time spent <150 mm Hg) was calculated as previously described.13

**Image Protocol**

Two hours after treatment initiation, all patients underwent a standard NCCT scan consisting of 5-mm slices (120 kVp; 300 mA/slice) through the whole brain (18–20 slices; 512×512 matrix). A 38- to 80-mm-thick section, centered on the NCCT slice with the greatest hematoma diameter, was selected for perfusion assessment. CTP slab thickness and acquisition protocol varied according to scanner capabilities. Intravenous iodinated contrast (Iohexol, 40–50 mL) was administered at rates of 4 to 7 mL/s via 18 gauge angiocatheter in an antecubital vein and CTP images (64–320 slices; 80 kvp; 200 mA/slice) were acquired every second for 50 s. The NCCT scan was repeated 24±3 hours after randomization.

![Figure 1. A](http://stroke.ahajournals.org/)

Example of regions of interest: perihematoma region (left), external borderzone (middle), and internal borderzone (right). Maps of cerebral blood flow (CBF), volume (CBV), and mean transit time (MTT) from patients randomized to a target systolic blood pressure of <160 mm Hg (B) and <150 mm Hg (C). Borderzone regions not shown on the perfusion maps for clarity.

**Image Analysis**

Image analysis was completed by 2 independent raters (B.G. and R.M.) blinded to BP treatment targets and clinical data. Hematoma, intraventricular hemorrhage and total ICH (hematoma+intraventricular hemorrhage) volumes were assessed on NCCT images using planimetric techniques. Raw CTP images were analyzed using the PerfiScape analysis package (PerfiScape 2.0 CT Stroke Edition; Olea Medical, Marseilles, France). Quantitative CBF, CBV, and mean transit time maps were derived from the tissue time–density curve, on a per-voxel basis over time, using a block recirculation deconvolution algorithm.14 Postprocessed perfusion maps were then transferred to the Analyze 11.0 software package (Biomedical Imaging Resource; Mayo Clinic) for region of interest analysis.15 An intensity threshold technique was used to define the perimeter of the hematoma on the precontrast CTP source image. A 1-cm perihematoma region, a contralateral homologous region, and bilateral internal and external borderzones were outlined as regions of interest that excluded intraventricular and subarachnoid spaces (Figure 1).16 All voxels containing blood vessels (CBF>100 mL/100 g/min or CBV>8 mL/100 g) were removed from regions of interest using an intensity threshold.17 In cases where the hematoma itself involved a borderzone, the latter was not outlined. We measured the volume of tissue in the internal the external borderzones, and the perihematoma region perihematoma region with perfusion below previously tested thresholds: CBF<18 or <12 mL/100 g/min.19,20 CBF<40% of mean

**Table 1. Baseline Characteristics of Randomized Patients**

<table>
<thead>
<tr>
<th>Age, y, mean±SD</th>
<th>Target (n=39)</th>
<th>Target (n=36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>70.7±12.5</td>
<td>68.7±11.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Randomized &lt;6 h</td>
<td>18 (46%)</td>
<td>17 (42%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (67%)</td>
<td>28 (78%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>4 (11%)</td>
<td>1 (3%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>6 (16%)</td>
<td>2 (6%)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**Clinical characteristics**

| Systolic BP, mm Hg, mean±SD | 182±20 | 184±25 | 0.60 |
| Diastolic BP, mm Hg          | 93±19  | 97±23  | 0.42 |
| Mean arterial pressure, mm Hg| 122±17 | 126±22 | 0.44 |
| Heart rate, bpm, mean±SD     | 76±15  | 79±18  | 0.53 |
| Glasgow Coma Scale, median (IQR) | 15 (4–15) | 15 (6–15) | 0.77 |
| NIHSS score, median (IQR)    | 2 (5%)  | 1 (3%)  | 1.0   |

**Hematoma volume**

| Basal ganglia | 29 (74%) | 27 (75%) | 0.99 |
| Lobar         | 9 (23%)  | 8 (22%)  | ... |
| Brain stem    | 1 (3%)   | 1 (3%)   | ... |
| Intraparenchymal hematoma volume, mL, mean±SD | 23.9±28.3 | 22.6±21.4 | 0.94 |
| Intraventricular extension | 13 (33%) | 16 (44%) | 0.35 |
| Intraventricular, mL, mean±SD | 2.1±6.1 | 4.2±8.8 | 0.23 |
| Total ICH volume, mL, mean±SD | 26.0±30.8 | 26.9±25.2 | 0.66 |

BP indicates blood pressure; ICH, intracerebral hemorrhage; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.
CBF in the contralateral homologous region (relative CBF<0.40)\textsuperscript{20}; CBV<2.5 mL/100 g\textsuperscript{20,21}; and mean transit time >6 s.\textsuperscript{20}

**Statistical Analysis**

The frequency of risk factors and clinical characteristics at baseline were compared using Pearson or Fisher exact \(\chi^2\) tests. Differences in BP between treatment groups were considered significant if the 95% confidence intervals did not overlap. The differences between treatment groups in critically hypoperfused tissue volume was assessed using independent samples \(t\) tests. Linear regression was used to assess the relationship between BP change or low SBP load, and volume of hypoperfused tissue. Statistical analyses were completed using SPSS (SPSS Statistics 20 Inc, 2008).

**Results**

**Patient Characteristics**

Seventy-five patients were enrolled between January 2007 and December 2011 and randomized to a BP treatment target of <150 mm Hg (n=39) or <180 mm Hg (n=36). Two patients from the <150 mm Hg group were excluded from the analysis because of lack of analyzable CTP. The groups did not differ with respect to baseline demographics, BP, hematoma location or volume, or time from symptom onset to randomization (Table 1). The cause of ICH was hypertensive in 53 (73%) patients, anticoagulant-associated ICH in 4 (5%) patients, and unknown in 16 (22%) patients.

**BP Treatment Effects**

All patients in the <150 mm Hg group and 44% of patients in the <180 mm Hg group were treated with intravenous anti-hypertensive medication. At the time of the CTP, mean SBP in the <150 mm Hg group (140±19 mm Hg) was significantly lower than that in the <180 mm Hg group (162±12 mm Hg; \(P<0.001\)). Weighted average SBP was lower in the <150 mm Hg target group (148.1±11.5 mm Hg) than in the <180 mm Hg (163.1±13.5 mm Hg; \(P<0.001\)). Low SBP load was also lower in the <150 mm Hg target group (58%) than in the <180 mm Hg group (24%; \(P<0.001\)).

**Borderzone Perfusion and Ischemic Thresholds**

The mean CBF in the internal borderzone ipsilateral to the hematoma (32.5±13.9 mL/100 g/min) was not lower than that in the contralateral hemisphere (34.3±12.7 mL/100 g/min; \(P=0.054\)). Similarly, CBF in the ipsilateral external borderzone (40.1±11.6 mL/100 g/min) was not lower than in the contralateral external borderzone (41.3±12.1; \(P=0.17\)). Mean CBF in the internal borderzones was similar in both the ipsilateral (30.5±12.9 versus 33.1±15.9 mL/100 g/min) and contralateral (33.7±11.5 versus 35.6±14.2 mL/100 g/min) hemispheres of patients in both BP treatment groups (<150 and <180 mm Hg, respectively).

The mean percentage volume of total borderzone tissue with CBF<18 mL/100 g/min (<150 mm Hg group, 14.7±13.6% versus <180 mm Hg group, 15.6±13.7%; \(P=0.78\)) or CBF<12 mL/100 g/min (<150 mm Hg group, 4.2±5.9% versus <180 mm Hg group, 5.9±9.1%; \(P=0.34\)) did not differ between treatment groups. The same was true for mean CBF<40% mean contralateral CBF (<150 mm Hg group, 13.9±10.5% versus <180 mm Hg group, 10.9±7.5%; \(P=0.17\))

**Table 2. Effects of Blood Pressure Reduction on Hypoperfused Tissue Volume**

<table>
<thead>
<tr>
<th></th>
<th>&lt;150 mm Hg Target (n=37)</th>
<th>&lt;180 mm Hg Target (n=36)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % volume of internal borderzone tissue with CBF&lt;18 mL/100 g/min</td>
<td>14.9±17.3</td>
<td>17.9±19.9</td>
<td>0.50</td>
</tr>
<tr>
<td>Mean % volume of internal borderzone tissue with CBF&lt;12 mL/100 g/min</td>
<td>4.2±5.9</td>
<td>5.9±9.1</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean % volume of internal borderzone tissue with CBV&lt;2.5 mL/100 g</td>
<td>36.0±14.8</td>
<td>42.0±18.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Mean % volume of internal borderzone tissue with MTT&gt;6 s</td>
<td>40.0±17.2</td>
<td>38.2±16.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean % volume of external borderzone tissue with CBF&lt;18 mL/100 g/min</td>
<td>14.2±12.7</td>
<td>14.7±11.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean % volume of external borderzone tissue with CBF&lt;12 mL/100 g/min</td>
<td>5.2±5.0</td>
<td>5.6±6.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean % volume of external borderzone tissue with CBV&lt;2.5 mL/100 g</td>
<td>53.3±25.2</td>
<td>56.2±26.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Mean % volume of external borderzone tissue with MTT&gt;6 s</td>
<td>40.0±17.1</td>
<td>37.4±15.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Mean % volume of perihematoma tissue with CBF&lt;18 mL/100 g/min</td>
<td>17.5±15.4</td>
<td>16.5±14.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean % volume of perihematoma tissue with CBF&lt;12 mL/100 g/min</td>
<td>7.0±7.2</td>
<td>6.6±7.6</td>
<td>0.85</td>
</tr>
<tr>
<td>Mean % volume of perihematoma tissue with CBF&lt;40% mean contralateral CBF</td>
<td>13.9±10.5</td>
<td>10.9±7.5</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean % volume of perihematoma tissue with CBV&lt;2.5 mL/100 g</td>
<td>33.4±10.3</td>
<td>37.0±12.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean % volume of perihematoma tissue with MTT&gt;6 s</td>
<td>44.9±15.2</td>
<td>42.3±15.0</td>
<td>0.48</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow; CBV, cerebral blood volume; and MTT, mean transit time.
watershed tissue regions in patients with acute ICH indicate that although CBF is below ischemic thresholds in small portions of borderzone regions, this volume of hypoperfused tissue is not affected by acute BP reduction. Similar results were also found within the perihematoma region. This is also the first analysis of the effect of low SBP load on perfusion thresholds in patients with ICH. We found no relationship between the amount of time SBP was controlled (<150 mmHg) and the volume of tissue reaching critical perfusion thresholds. These data do not provide support for the hypothesis that aggressive BP reduction is causally related to the development of borderzone ischemic lesions.

### Borderzone Perfusion

Although the mean CBF within internal and external borderzones was similar to that of the rest of the contralateral hemisphere, we did find that 15% of the tissue in these regions was below the ischemic threshold of 18 mL/100 g/min. The significance of this apparent hypoperfusion is unclear, but may be relevant, given evidence from MRI studies of subacute ischemia, remote from the hematoma, in 14% to 41% of patients. These ischemic lesions have been reported to be more frequent in patients with lower baseline BP and after aggressive BP reduction. These same reports also indicate that diffusion-weighted imaging lesions are often present within watershed/borderzone vascular territories, suggesting a hemodynamic mechanism. These investigators hypothesize that lower cerebral perfusion pressure after BP reduction results in ischemia within the most vulnerable tissue at the borderzones between major cerebral arteries. Our results do not lend support to this hypothesis, but it is possible that flow in these regions falls subacutely, leading to diffusion-weighted imaging lesion development beyond the time period included in our study. This can only be effectively addressed with serial assessments of CBF, which are not feasible with available perfusion measurement techniques.

### Discussion

The results of this first study of perfusion thresholds within watershed tissue regions in patients with acute ICH indicate

<12 mL/100 g/min (5.1±5.1% versus 5.8±6.8%; P=0.62) did not differ between treatment groups. The same was found when internal and external borderzones were assessed separately (Figure 2A and 2B). The percentage volume of borderzone tissue below the regional CBF threshold of 0.40 was also similar in the <150 mmHg (5.1±3.4%) and <180 mmHg treatment groups (5.8±4.1%; P=0.45).

### Perihematoma Region Perfusion Thresholds

In all 73 patients, the perihematoma region had a mean CBF of 38.7±11.9 mL/100 g/min and was hypoperfused relative to the contralateral homologous region (regional CBF=0.87±0.01). A small amount of the perihematoma region reached ischemic CBF thresholds of <18 mL/100 g/min (17.0%) and <12 mL/100 g/min (6.8%). However, the mean percentage volume of perihematoma tissue with CBF <18 (<150 mmHg group, 17.5±15.4% versus <180 mmHg group, 16.5±14.3%; P=0.76) or <12 mL/100 g/min (7.0±7.2% versus 6.6±7.6%; P=0.85) did not differ between treatment groups (Figure 2C). The percentage volume of perihematoma tissue with regional CBF <0.40, CBV<2.5 mL/100 g, or mean transit time >6 s also did not differ between treatment groups (Table 2).

### BP Changes and Hypoperfused Tissue Volume

Linear regression demonstrated no relationship between the change in systolic BP and the percentage of borderzone tissue included in our study. This can only be effectively addressed with serial assessments of CBF, which are not feasible with available perfusion measurement techniques.

Figure 3. Linear regression plots of the relationship between the change in systolic blood pressure (SBP) between randomization and the time of the computed tomographic (CT) perfusion scan and the volume of borderzone (A) or perihematoma (C) tissue below 2 cerebral blood flow (CBF) thresholds. No relationship was seen between low SBP load (the fraction of time between randomization and CT perfusion with SBP<150 mmHg, which has been binned in 12.5% increments), and the percentage of borderzone (B) or perihematoma (D) tissue with CBF <18 or <12 mL/100 g/min. Error bars, SEM.
one other study have shown that BP reduction does not exacerbate this decrease in mean perihematoma CBF.3,25 However, neither study addressed the possibility that while mean CBF remained unchanged, portions of the perihematoma region may have dropped below thresholds for ischemia and infarction. We have found that small portions of the perihematoma region are actually critically hypoperfused, which may be related to MRI observations consistent with limited areas of potentially ischemic tissue.23 From a therapeutic perspective, it is important to note that the volume of hypoperfused tissue does not change with aggressive BP reduction. This is consistent with larger clinical trials demonstrating no adverse effects when BP is lowered.26,27

Limitations
This study is limited by the assessment of cerebral perfusion at a single time point (2 hours after treatment initiation). This time point was chosen to ensure BP stability at the assigned target before perfusion assessment; however, we cannot eliminate the possibility of earlier or later ischemic changes secondary to BP reduction. Although the study protocol limited antihypertensives to 3 agents (labetalol, hydralazine, and enalapril), it is possible that different drugs may have had different effects on BP over time. Furthermore, unaccounted physiological factors, such as heart rate, body temperature, or glucose metabolism, may influence cerebral perfusion over time.

The use of multiple CT scanners may have resulted in differences in CTP acquisition. However, all image analyses were performed at a central core imaging laboratory using a single analysis software protocol for ischemic thresholds. Because validation studies of CTP-derived CBF values are limited to animal models28 and have not been completed in patients with acute stroke, quantitative CTP data indicating hypoperfusion may not be accurate in all cases. Nonetheless,
our relative CBF measurements confirm that there is tissue with lower flow in these patients. Conclusions based on our results would, however, be strengthened if an MRI study had been included in the ICH ADAPT protocol. Limitations also include the relatively small sample size and the heterogeneity of hematoma size and location (lobar and deep). All patients presented with acutely elevated BP; however, and 70% had an underlying diagnosis of hypertension.

Conclusions
Small volumes of tissue with perfusion characteristics below ischemic thresholds are found in patients with acute ICH. Aggressive BP reduction does not increase the volume of critically hypoperfused tissue in the internal and external borderzone or perihematoma regions. These results provide further reassurance that acute BP reduction in ICH is safe, but the possibility that CBF changes contribute to the formation of subacute diffusion-weighted imaging lesions cannot be excluded without serial measurements of CBF and randomized studies with an MRI end point.

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Disclosures
None.

References
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